Acute Renal Failure Resulting from Intravenous Immunoglobulin Therapy

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Abstract

Intravenous administration of immunoglobulin is used for the treatment of many conditions, including primary immunodeficiency states, autoimmune disorders, glomerulonephritides and polyneuropathy.[1-10] Acute renal failure induced by intravenous immunoglobulin is a known but rare adverse reaction. We have a patient who was treated with IVIG for inflammatory polyneuropathy. Intravenous immunoglobulin therapy 0.5 g/kg/d was given for 4 days. Three days after completion of IVIG therapy, patient developed decreased urine output. His serum creatinine increased from baseline of 1.3 to 7 mg/dL. Even though IVIG was discontinued, patient required hemodialysis. This case illustrated that IVIG can cause acute oliguric renal failure which is reversible after withdrawal of the drug. Risk factors include pretreatment renal impairment, diabetes mellitus, high concentration of sucrose or glucose in IVIG preparation and older age. Awareness of this serious side effects and recognition of predisposing factors provide means of avoiding a known life threatening complication of IVIG therapy.

Case report

A 76-year-old Chinese male with a history of inflammatory polyneuropathy was admitted for acute renal failure following treatment with IVIG. The patient has been well until one year earlier when he developed progressive lower extremities weakness. He was seen by a neurologist and inflammatory polyneuropathy was diagnosed based on a nerve conduction study. The patient was admitted by his neurologist for IVIG injection (Panglobulin, ZLB). He was hospitalized for 4 days and received IVIG treatment with the dose of 2 mg/kg for maximal rate of 100 ml/h. The admitting serum creatinine was 1.3mg/dl. On the third day of the treatment with IVIG, creatinine increased to 1.5mg/dl. The patient was discharged 3 days before this admission. For two days prior to the second admission, the patient noted decreased urine output. The patient also developed fatigue with anorexia. Because of those symptoms, he was evaluated in the emergency room and was found to have acute renal failure with a serum creatinine of 7.0mg/dL and BUN of 71 mg/dL. Aside from fatique, he denies having nausea, pruritus or shortness of breath. He denies the use of over-the-counter pain medications. The patient has a history of diabetes type II for more than 15 years, hypertension, chronic obstructive pulmonary disease and coronary artery disease.

The results of an extended physical examination was significant for elevated blood pressure of 171/71 mmHg; lung examinations were normal. Heart examination revealed normal sinus rhythm, no pericardial rub, no murmur audible. The patient had no asterixes. The neurological examination was remarkable for muscle strength grade 5/5 in the upper extremities, 4/5 of both iliopsoas, 2/5 of gastrocnemius and tibialis anterior muscles, mild atrophy of calf and hyporeflexia of both lower extremities, negative Babinski's sign bilaterally.

A renal ultrasonography was performed which showed right kidney 10.1 cm in diameter, left kidney 11.2 cm with 1.3cm cyst at lower pole of left kidney without hydronephrosis.

Foley's catheter was inserted in the emergency room which yielded only 10ml of urine. Furosemide 50 mg was given intravenously without response, followed by continuous intravenous infusion drip with the rate of 30mg/hr without response. The patient had peak serum creatinine of 8.8mg/dl. On the third day of the admission, acute hemodialysis was performed because of anuria and uremia. Shortly after dialysis, on the fourth day of hospitalization, his urine output increased and eventually became polyuric. Serum creatinine continued to improve throughout the hospitalization. The patient was discharged on the seventh day of hospitalization with serum creatinine of 2.4mg/dl. He was followed by the nephrologist as an out-patient with clinical improvement of serum creatinine back to baseline.

Discussion

IVIG induced acute renal failure was first described in 1987.[11] In review of case series, most of the patients had a small and transient elevation in the plasma creatinine concentration that may reflect a reduction in creatinine secretion rather than the fall in glomerular filtration rate.[9] In the group of patients who developed acute renal failure, 48 % were more than 65 years old and in 57% of them there was preexisting renal disease such as diabetes and renal insufficiency.[1,4-6,9]

Between 1985-1998, the Federal Drug Administration received a total of 120 reports of adverse renal events (acute renal failure and renal insufficiency) associated with high dose IVIG therapy. On review of these reports 90% of the patient had

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received sucrose containing IVIG: Sandoglobulin and Panglobulin (combined responsible for 69% of all cased in the United States), Gammar-P.I.V. and Gammar-I.V.b.(were responsible for 22 percent of the cases) Fifty – nine percent had diabetes mellitus and 26% had pretreatment renal impairment. All renal adverse events occurred in the first 7 days following the administration of IVIG therapy.[12,13] In our case, the temporal relationship between acute renal failure and IVIG administration was consistent with that seen in previous reports, there was no other apparent cause for the acute renal failure.

The mechanism of IVIG induced acute renal failure was previously thought to be due to aggregated immunoglobulin complex. However, as series of typical histological findings of renal biopsy in these patient showed vacuolization and swelling of tubular and glomerular cells has drawn attention to the high concentration of carbohydrate additive in IVIG. Sucrose is the main carbohydrate which is added to IVIG as a stabilizing agent. Uptake of filtered sucrose by proximal tubular cells leads to osmotic water entry and cell swelling which is called " osmotic nephrosis".[6,14,15]

Osmotic injury by sucrose is the leading hypothesis for IVIG induced acute renal failure, however, there are some arguments against this mechanism since the patient do not present with true hypertonic syndrome. The hypertonic IVIG solutions are quickly diluted in blood. Furthermore, if it was the tonicity causing tubular damage, one would expect to see more severe lesions in the distal proximal tubule where the osmolality due to reabsorption of water and sodium is the highest. But histologic examination indicated that proximal segment of the proximal tubule was the part with the most damage. Also, based on animal studies, it is unlikely that carbohydrate alone can cause severe impairment of kidney function. Some underlying renal disease or drug affecting renal function or hemodynamics seem to be important contributing factors for the development of acute renal failure. Healthy rats treated with high dose mannitol alone did not developed renal failure. Only after concomitant administration of cyclosporin and IV mannitol did the animal develop marked deterioration in renal function and osmotic nephrosis on histology. A similar observation with severe oliguric acute renal failure was noted in a human kidney graft recipient on cyclosporin, in whom a large amount of mannitol had been injected intravenously. Lately, non-sucrose containing IVIG preparation have been used successfully in patients with previous history of IVIG-associated acute renal failure.

Acute renal failure occurred in most cases during first exposure to IVIG. The clinical manifestation varies from asymptomatic rise in plasma creatinine concentration to anuric acute renal failure requiring hemodialysis. Risk factors for IVIG – induced acute renal failure include including age more than 65, those with preexisting renal insufficiency, diabetes mellitus, volume depletion or those who receiving nephrotoxic drug. Spontaneous resolution typically occurs within 4-8 days after discontinuation of IVIG. Identification of patients who are at risk for developing acute renal failure caused by IVIG.

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